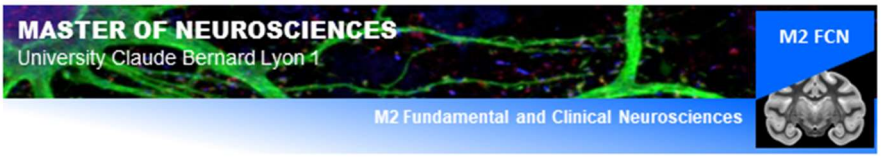

MASTER 2 Fundamental and Clinical Neurosciences

Internship proposal 2024-2025

(internship from January to June 2025)

Host laboratory:
Centre de Recherche en Neurosciences de Lyon
Inserm U1028, CNRS UMR5292, Université Lyon 1
Centre Hospitalier Le Vinatier – Bât. 462 NeuroCampus
95, Boulevard Pinel - 69500 Bron

Host team :
Equipe GENDEV – Génétique des anomalies du neurodéveloppement
https://www.crnl.fr/fr/equipe/gendev

Internship supervisors : DELOUS Marion, marion.delous@inserm.fr

Project title : Deciphering the physiopathological mechanisms of microcephalic syndromes linked to defective minor splicing

Project summary :
Splicing of pre-messenger RNAs is a crucial step in gene expression. For the majority of species, it is ensured by two distinct machineries, the major and minor spliceosomes. In 2011, the GENDEV team showed that mutations in the U4atac component, specific to the **minor spliceosome** that removes minor introns in ~750 genes in the human genome, are responsible for the **microcephalic** dwarfism syndrome, called Taybi-Linder (TALS). Recently, it is another clinical entity that the team uncovered associated to u4atac : an atypical Joubert syndrome (JBTS), a well-known ciliopathy with cerebral anomalies, which suggests an unexpected link between TALS, minor splicing and **the primary cilium**. To understand the pathophysiological mechanisms of these syndromes, and why different mutations in the *RNU4ATAC* gene lead to phenotypic variability, the team has developed different models. During his/her internship, the student will study either **the zebrafish model** or the **induced pluripotent stem cells (iPSC)-derived cortical organoids and perform cellular and molecular approaches**. The objective of the internship will be the characterization of the cerebral anomalies (global morphology of brain structures and cellular processes known to be involved in microcephaly). This approach, mostly based on confocal imaging, will be combined to analyses of molecular aspects, i.e. retention of minor introns in candidate genes (qRT-PCR).

3-5 recent publications:
- Guguin J, *et al.* A TALS-like associated *RTTN* mutation impedes neural rosette formation in human cortical organoids. medRxiv doi: https://doi.org/10.1101/2024.04.03.24303866 (**2024**)
- Khatri D, *et al*. Deficiency of U4atac snRNA results in ciliary defects. *PNAS* 120(9):e2102569120 (**2023**)
- Benoit-Pilven C, *et al*. Clinical interpretation of variants identified in *RNU4ATAC*, a non-coding spliceosomal gene. *PLoS One*, 15(7):e0235655 (**2020**)
- Cologne A, *et al*. New insights into minor splicing - A transcriptomic analysis of cells derived from TALS patients. *RNA* 25(9):1130-1149 (**2019**)
- Putoux A, *et al*. Refining the phenotypical and mutational spectrum of Taybi-Linder syndrome. *Clin Genet* 90(6):550-555 (**2016**)